P1 1004616

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

May 05, 2003

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *60/372,005*
FILING DATE: *April 12, 2002*
RELATED PCT APPLICATION NUMBER: *PCT/US03/11100*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

N. WOODSON
Certifying Officer

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

04-15-02 A/PRO

Please type a plus sign (+) inside this box → [+]

PTO/SB/16 (02-01)
Approved for use through10/31/2002. OMB 0651-0032
U S Patent and Trademark Office; U S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

jc887 U.S. PTO 04/12/02

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EL 781455715 US

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Kevin John	Williams	425 Wister Road Wynnewood, PA 19096

☐ *Additional inventors are being named on the ___ separately numbered sheets attached hereto*

11040 U.S. PTO 60/377005 04/12/02

TITLE OF THE INVENTION (280 characters max)

THERAPEUTIC USES OF UVA

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☒ Customer Number 03000 → Place Customer Number Bar Code Label Here

OR *Type Customer Number here*

☒ Firm or Individual Name: Caesar, Rivise, et al. 03000 PATENT TRADEMARK OFFICE

Address					
Address					
City		State		ZIP	
Country		Telephone		Fax	

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* 16
☒ Drawing(s) *Number of Sheets* 1
☑ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number
☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ Applicant claims small entity status. See 37 CFR 1.27.
☐ A check or money order is enclosed to cover the filing fees
☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 03-0075
☐ Payment by credit card. Form PTO-2038 is attached.

FILING FEE AMOUNT ($): 80.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE Allan H. Fried

Date 4/12/02

TYPED or PRINTED NAME Allan H. Fried

REGISTRATION NO. *(if appropriate)* 31,253

Docket Number: W1107/20001

TELEPHONE 215-567-2010

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

Applicant : Kevin John Williams

Invention : Therapeutic Uses UVA

This is a provisional patent application which includes the following:

1. Provisional Application for Patent Cover Sheet, in duplicate
2. Specification – 12 pages
3. 22 Claims – 3 pages
4. Abstract – 1 page
5. Drawings - 1
6. Return Receipt Postcard

"Express Mail" Mailing Label No. **EL781455715US**

Date of Deposit April 12, 2002

I hereby certify that the above-identified documents are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and are addressed to the Commissioner for Patents, Box PROVISIONAL PATENT APPLICATION, Washington, D.C. 20231

Allan H. Fried

TITLE OF THE INVENTION:

THERAPEUTIC USES OF UVA

BACKGROUND OF THE INVENTION

The present invention relates to the use of UVA irradiation to enhance the effectiveness of the body's immunologic response against abnormal cells, infecting cells, infected cells, infectious agents, and other medically relevant targets.

The history of UVA treatment (normally radiation in the range 320 nm to 400 nm) against certain non-infectious diseases, in particular lupus erythematosus and scleroderma, which are autoimmune diseases, and eczema and mastocytosis, suggests that the result of UVA treatment is a diminishment of the immune response, for example including a reduction in active immune cells.

An invention presented here is, nevertheless, the use of low levels of UVA to combat abnormal cells, such as papilloma virus-infected cells (as in warts), other types of precancerous cells, and cancerous cells.

Some success had been reported for the use of UVA radiation to prepare the body to fight a subsequent infection, that is, as a purely preventive approach. Nonetheless, such an approach is of nearly no utility, because it is not practical to treat large numbers of subjects who may or may not become subsequently exposed to an infectious agent. In contrast, an invention presented here is the use of low levels of UVA to treat an existing infection.

There have been efforts to develop creams and ointments for application onto the skin for the purpose of altering local expression of cytokines in the treatment of certain conditions. There is a need, however, to develop methods that provide better penetration

and therefore better depth of effect. The current invention addresses these needs.

Furthermore, to facilitate the implementation of those and related inventions, a device that allows precise control of UVA radiation is disclosed.

BRIEF SUMMARY OF THE INVENTION

Use of UVA with abnormal cells

In a first general aspect, the invention is a method for treating a condition characterized by the presence of abnormal cells in a person or animal, said method comprising the step of irradiating said abnormal cells and/or nearby tissue (within 5 cm of the perimeter of radiation) of the person or animal with UVA radiation (from part or all of the 320-500 nm range, preferably from part or all of the 320-400 nm range) at a tissue surface dose in the range 1 to 15 Joules/m^2 within a 2-hour period (either by continuous or interrupted administration), wherein the condition is selected from the group consisting of a neoplastic condition, a proliferative condition, a precancerous lesion, a condition treated by an interferon or compound or procedure that induces an interferon, and a virus-caused condition.

It is understood that repeated administration (for example, 3 times per week for 2 weeks) of doses of 1 to 15 joules/m^2 as described herein will be desirable for treatment.

Regarding that first general aspect of the invention, a number of specific embodiments are of particular interest, either alone or in combination. They include but are not limited to the following:

1) the dose is in the range 3 to 10 J/m^2;

2) the dose per unit time is in the range to deliver 5 J/m^2 in 30 seconds to 30 minutes (*i.e.,* 1-60 min for 10 J/m^2);

3) the surface area of tissue irradiated is at least 0.3 cm^2;

4) the surface area of tissue irradiated is not more than 50 cm^2;

5) the abnormal cell is in the path of irradiation; and

6) the abnormal cell is outside the perimeter of the path of irradiation but is within 5 cm of said perimeter; and

7) the UVA radiation is UVA1 radiation (from part or all of the 340 nm – 400 nm range).

<u>Use of UVA with infections</u>

In a second general aspect, the invention is a method for treating an infectious condition in a person, said method comprising the step of irradiating tissue of that person with UVA irradiation (from part or all of the 320-500 nm range, preferably from part or all of the 320-400 nm range) at a tissue surface dose in the range 1 to 15 J/m^2 (more preferably 1 to 7.5 J/m^2, most preferably 1 to 5 J/m^2) within a 2-hour period, wherein infecting cells are in the tissue.

Regarding that second general aspect of the invention, a number of specific embodiments are of particular interest, either alone or in combination. They include but are not limited to the following:

1) the dose is in the range 3 to 10 J/m^2;

2) the dose per unit time is in the range to deliver 5 J/m^2 in 30 seconds to 30 minutes (*i.e.,* 45 sec to 45 min for 7.5 J/m^2);

3) the surface area of tissue irradiated is at least 0.3 cm^2;

4) the surface area of tissue irradiated is not more than 50 cm^2

5) infected cells and/or an infectious agent is in the path of irradiation;

6) the UVA radiation is UVA1 radiation (from part or all of the 340 nm – 400 nm range).

Use of UVA with inflammatory conditions

In a third general aspect, the invention is a method of treating an inflammatory condition, said method comprising the step of irradiating such tissue of the person with UVA radiation (from part or all of the 320-500 nm range, preferably from part or all of the 320-400 nm range) at a tissue surface dose in the range 1 to 15 J/m^2 within a 2-hour period.

Regarding this aspect of the invention, a number of specific embodiments are of particular interest, either alone or in combination. They include but are not limited to the following:

1) the dose is in the range 3 to 10 J/m^2;

2) the dose per unit time is in the range to deliver 5 J/m^2 in 30 seconds to 30 minutes (*i.e.*, 1-60 min for 10 J/m^2);

3) the surface area of tissue irradiated is at least 0.3 cm^2;

4) the surface area of tissue irradiated is not more than 50 cm^2;

5) the inflamed area is in the path of irradiation;

6) the inflamed area is outside the perimeter of the path of irradiation but is within 5 cm of said perimeter;

7) the UVA radiation is UVA1 radiation (from part or all of the 340 nm – 400 nm range).

Use of UVA with vascular conditions

In a fourth general aspect, the invention is a method for treating a vascular condition, said method comprising the step of irradiating vascular tissue of the person with UVA radiation (from part or all of the 320-500 nm range, preferably from part or all of the 320-400 nm range) at a vascular tissue surface dose in the range 1 to 15 J/m^2 within a 2-hour period, Regarding this aspect of the invention, a number of specific embodiments are of particular interest, eiither alone or in combination. They include but are not limited to the following:

1) the dose is in the range 3 to 10 J/m^2;

2) the dose per unit time is in the range to deliver 5 J/m^2 in 30 seconds to 30 minutes (*i.e.,* 1-60 min for 10 J/m^2);

3) the surface area of tissue irradiated is at least 0.3cm^2;

4) the surface area of tissue irradiated is not more than 50 cm^2;

5) the vascular condition is in the path of irradiation;

6) the vascular condition is outside the perimeter of the path of irradiation but is within 5 cm of said perimeter;

7) the UVA radiation is UVA1 radiation (from part or all of the 340 nm – 400 nm range).

Application to other animals

The inventions described herein are primarily intended for use with humans, but they can also be applied to other animals, including, but not limited to pets, farm animals, sport animals (*e.g.,* race horses and racing dogs), and other commercially

significant animals.

Device for regulating UVA radiation

In another general aspect, the invention is a device for regulating UVA radiation to a tissue, said device comprising:

(a) a source of UVA light;

(b) a UVA detector; and

(c) a regulatory means.

wherein the input to said regulatory means comprises a preset desired UVA dose/m^2 and/or a preset desired UVA dose/m^2/time; additional optional inputs to said regulator means include the distance from source to detector and distance from source to target treatment area, in situations when the source is mobile and the two distances may not be the same; and

wherein the output from said regulatory means is transmitted to the source of UVA light so as to achieve the desired UVA dose/m^2 and/or preset desired UVA dose/m^2/time.

In a preferred embodiment, the device permits the source of UVA light to be alternately directed at the UVA detector and a target area in or on a person. Direction at the UVA detector can be used to calibrate the light source and can be done before each use or, say, once a week. In a preferred embodiment for a device for irradiating a small target area, the device includes a mask to shield extraneous areas from radiation exposure, and said mask can incorporate a detector. In a preferred embodiment for a

device irradiating a very large target area, such as whole-body surface irradiation (*e.g.*, a light box), a detector can be incorporated into a wall of said light box

As to all UVA or UVA1 radiation denoted herein, the radiation may administered over the entire range of wavelengths or within a narrow band of wavelengths as created, for example by a laser.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is a schematic view of a device of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Neoplastic conditions that are targets for the present invention include, but are not limited to, a skin cancer, a cancer of a mucous surface, a cancer of an epithelial surface, a melanoma, a basal cell cancer, a squamous cell cancer, a Kaposi's sarcoma, and an adenocarcinoma.

Proliferative conditions that are targets for the present invention include, a keloid, an actinic keratosis, a polyp, a hemangioma, and a condition treated by an interferon or a compound or procedure that induces an interferon.

Pre-cancerous lesions that are targets for the present invention include, but are not limited to, an actinic keratosis, a polyp, a condition treated by an interferon or a compound or procedure that induces an interferon, and a viral infection. Said viral infection includes,

but it not limited to, a papilloma virus infection, a herpes virus infection, and a retroviral infection.

Virus-caused abnormal cell conditions that are targets for the present invention include, but are not limited to, warts (caused by papilloma virus) molluscum contagiosum (caused by a pox virus), Kaposi's sarcoma (caused by human herpes virus-8), herpes simplex (caused by human herpes viruses-1 and –2), herpes zoster (caused by the varicella zoster virus), and a condition treated by an interferon or a compound or procedure that induces an interferon, by way of examples.

Warts include, but are not limited to, "verruca vulgaris", which is a term generally referring to lesions outside the groin, and "condyloma", which is a term generally referring to lesions in the groin area. Locations of warts can be anywhere on the skin (most commonly hands, feet, penis, and vulva), as well as mucous membranes including, but not limited to, the anus, the vulva, the vagina, the uterine cervix, and the mouth.

Infectious conditions that are targets for the present invention include, but are not limited to, leishmaniasis, a parasitic infection, an infection by an intracellular organism, a fungal infection, a granulomatous disease, herpes infection, a papilloma virus infection, a wart, a cytomegalovirus infection, a mycobacterial infection, an atypical mycobacterial infection, an MAI infection, a bacterial infection, a viral infection, a slow viral infection, a prion infection, a spirochete infection, Lyme disease, an HIV-related infection, a Kaposi's sarcoma and an infection treated by an interferon or a compound or procedure that induces an interferon. As regards location, infectious conditions of particular interest are a cutaneous infection, an infection of a mucous membrane, a genital infection, an oral infection, an infection involving an epithelial surface (including, but not limited to, the

gastrointestinal epithelium and the genitourinary epithelium), a nasal infection, a cervical infection, and a penile infection.

Leishmaniasis of particular interest is one selected from the group consisting of L. mexicana, L. major, L. donovani, L. amazonensis, a Leishmania species that infects humans, a leishmania species that causes cutaneous disease, a Leishmania species that causes visceral disease, and a Leishmania species that infects an animal.

Inflammatory conditions that are targets for the present invention include, but are not limited to, psoriasis, and an inflammatory bowel disease. Inflammatory bowel disease includes, but it not limited to, Crohn's disease and ulcerative colitis.

Vascular conditions that are targets for the present invention include, but are not limited to, hemangioma and a vascular condition associated with HIV infection.

It is expected that UVA will be useful in the treatment of any disease or condition where increasing IL-12, increasing IFN-γ, shifting from TH-2 to TH-1, and/or suppressing TNFα secretion would provide benefit.

It can be seen from the foregoing that the irradiated tissue may be skin or internal tissue, such as the gastrointestinal tract, genitourinary tract, or internal organs.

UVA sources and detectors and intensity regulators

One of many commercially available UVA sources is the Berger Solar Simulator, which can for example be used with a 3-mm thick 345 mm Schott filter to get rid of UVB and UVA2, or used with window glass to get rid of UVB but not UVA2. Additionally, UVA fluorescent bulbs can be obtained from many companies. Lasers that generate wavelengths within the UVA or UVA1 ranges can also be used. Possible types of light

sources also include fluorescent bulbs, fluorescent bulbs with filters, lasers, solid-state devices, and incandescent sources with filters.

For irradiation of internal organs, the UVA source can be at the tip of a rigid or flexible tube. Alternatively, a rigid or flexible waveguide or waveguides can be used to deliver light internally, while the source is external. Alternatively, a rigid tube, such as a uterine speculum or a sigmoidoscope, can allow access of light to a target area. Illustrative, but not limiting, examples include irradiation of the uterine cervix and irradiation of the anus and sigmoid rectum in the treatment of conditions affecting those and nearby locations. An example of such a condition includes, but is not limited to, warts.

UV detectors that can be used to detect UVA light are also available from many companies. If the detector is sensitive to both UVA and UVB light, filters can be used to make it UVA specific (or UVA1 specific). The Solarmeter model 5.0 can be used. Ultralight also sells UV detectors.

Detectors measure the power output per unit area (*e.g.*, in units of mW/cm^2), which is a measure of intensity at a given distance from a source. From this number, one can calculate how long it will take to achieve a desired dose (one watt: one joule/second). Alternatively, a device for regulating UV radiation, described above, can be constructed to calculate this automatically.

The design of UVA regulators (including computerized ones) that take input as to desired intensities or amounts and also input as to actual intensities and time, are well within the skill of the art.

EXAMPLE

The Example is intended to illustrate the invention rather than limit it.

Example of device of the invention

A device of the invention can be understood by reference to Figure 1. In Figure1, a single source of UVA irradiation **1** and **1'** is shown at two positions where it creates UVA radiation beams **3** and **3'** respectively. In its first position, the beam irradiates an area **9** on the sole of a foot **11**. Within the area **9** is a wart **13**. If the source of UVA irradiation is swiveled about the axis **15** to its second position, denoted by **1'**, the beam impinges on a UVA detector **19**. A rigid rod **5** can be used to position the foot and the detector, respectively, relative to the UVA source, thereby ensuring that the foot and the detector are at the same distance from the UVA source when they are irradiated. Equivalently, the detector can be the moving component, swinging on a rigid rod where the foot **11** is, and back again to its original position, again ensuring that the foot and the detector are at the same distance from the UVA source when they are irradiated.

The device in Figure 1 is for a UVA source with a well-defined cross section. The size of the cross section of the beam can be further controlled by interposing, between the UVA source and its targets (foot and detector), a barrier with two apertures of identical size that allow identical irradiation of the foot and the detector. Equivalently, the detector can be incorporated into the barrier itself, next to or nearby to a single aperture that allows UVA to reach the foot.

A UVA regulator **21** receives from a person, or other source, input as to the intensity and amount of radiation that is desired for the sole of the foot. The regulator also receives

as input, from the detector **19**, data on the amount of radiation that reaches the detector when the UVA source is at **1'**. Based on the desired intensity and/or amount of radiation, it sends, as output to the UVA source, a signal that causes the UVA source to provide the desired intensity and/or amount of radiation. When the UVA source is moved to position **1**, the intensity and amount (intensity x time) of radiation will be that desired. In a preferred embodiment, the intensity of the UVA source is kept fixed, and the regulator adjusts the time of exposure to achieve the desired dose (amount) of radiation.

The device therefore ensures that the correct radiation will be administered even if the UVA source's radiation intensity is different from that specified by the manufacturer. This is indeed a common circumstance, particularly because UVA sources change over their useful lifetime.

Although illustrated for the irradiation of a wart, the system clearly can be adapted to use for irradiation of other conditions, including ones involving internal organs.

CLAIMS:

1. A method for treating a condition characterized by the presence of abnormal cells in a person, said method comprising the step of irradiating said abnormal cells and/or nearby tissue of the person with UVA radiation (from part or all of the 320-500 nm range, preferably from part or all of the 320-400 nm range) at a tissue surface dose in the range 1 to 15 J/m^2 within a 2-hour period wherein the condition is selected from the group consisting of a neoplastic condition, a proliferative condition, a precancerous lesion, a condition treated by an interferon or a compound or procedure that induces an interferon, and a virus-caused condition.

2. The method of Claim 1 wherein the condition is a neoplastic condition.

3. The method of Claim 2 wherein the neoplastic condition is selected from the group consisting of a skin cancer, a cancer of a mucous surface, a cancer of an epithelial surface, a melanoma, a basal cell cancer, a squamous cell cancer, a Kaposi's sarcoma, and an adenocarcinoma.

4. The method of Claim 1 wherein the condition is a proliferative condition.

5. The method of Claim 4 wherein the proliferative conditions is selected from the group consisting of a keloid, an actinic keratosis, a polyp, a hemangioma, and a condition treated by an interferon or a compound or procedure that induces an interferon.

6, The method of Claim 1 wherein the condition is a precancerous lesion.

7. The method of Claim 6 wherein the precancerous lesion is selected from the group consisting of an actinic keratosis, a polyp, a condition treated by an interferon or a compound or procedure that induces an interferon, and a viral infection.

8. The method of Claim 1 wherein the condition is a virus-caused condition.

9. The method of Claim 8 wherein the virus-caused condition is selected from

the group consisting of a wart, molluscum contagiosum, Kaposi's sarcoma, herpes simplex, herpes zoster, and a condition caused by an interferon or a compound or procedure that induces interferon.

10. The method of Claim 9 wherein the virus-caused condition is a wart.

11. A method for treating an infectious condition in a person, said method comprising the step of irradiating tissue of that person with UVA irradiation at a tissue surface dose in the range 1 to 15 J/m^2 within a 2-hour period, wherein infecting and/or infected cells are in the tissue.

12. The method of Claim 11 wherein the infectious condition is selected from the group consisting of leishmaniasis, a parasitic infection, an infection by an intracellular organism, a fungal infection, a granulomatous disease, herpes infection, a papilloma virus infection, a wart, a cytomegalovirus infection, a mycobacterial infection, an atypical mycobacterial infection, an MAI infection, a bacterial infection, a viral infection, a slow viral infection, a prion infection, a spirochete infection, Lyme disease, an HIV-related infection, a Kaposi's sarcoma, and an infection treated by an interferon or a compound or procedure that induces an interferon.

13. The method of Claim 11 wherein the infectious condition is selected from the group consisting of a cutaneous infection, an infection of a mucous membrane, a genital infection, a genitourinary infection, an oral infection, an infection involving an epithelial surface, a nasal infection, a cervical infection, and a penile infection.

14. A method of treating an inflammatory condition, said method comprising the step of irradiating such tissue of the person with UVA radiation at a tissue surface dose in the range 1 to 15 J/m^2 within a 24-hour period.

15. The method of claim 14 wherein the condition is selected from the group

consisting of psoriasis, eczema, an atopic condition, and an inflammatory bowel disease.

16. A method for treating a vascular condition, said method comprising the step of irradiating vascular tissue of the person with UVA radiation at a vascular tissue surface dose in the range 1 to 15 J/m^2 within a 2-hour period.

17. The method of Claim 16 wherein the vascular condition is selected from the group consisting of a hemangioma and a vascular condition associated with HIV infection.

18. A device for regulating UVA radiation to a tissue said device comprising

(a) a source of UVA light;

(b) a UVA detector; and

(c) a regulatory means;

wherein the input to said regulatory comprises a preset desired UVA dose/m^2 and/or a preset desired UVA dose/m^2/time; and

wherein the output from said regulatory means is transmitted to the source of UVA light so as to achieve the desired UVA dose/m^2 and/or a preset desired UVA dose/m^2/time.

19. A device of claim 18 wherein the device permits the source of UVA light to be alternately be directed at the UVA detector and a target area in or on a person.

20. The method of claim 1 wherein the condition is a condition treated by an interferon or a compound or procedure that induces an interferon.

21. The method of Claim 20 wherein the condition treated by an interferon or a compound or procedure that induces an interferon is selected from the group consisting of a wart, a keloid, a skin cancer, an actinic keratosis, a lymphoma, a cutaneous lymphoma, a hemangioma, a Kaposi' sarcoma, and hepatitis.

22. The device of claim 18 wherein said regulatory means incorporates a computer chip.

ABSTRACT

Methods and devices for using low-dose UVA radiation to treat medical conditions such as a neoplastic condition, a proliferative condition, a precancerous lesion, a virus-caused condition, infections, a vascular condition, and aninflammatory condition are disclosed.

FIGURE 1